Section: Cardiothoracic Surgery

Original Research Article

N-ACETYLCYSTEINE FOR THE PREVENTION OF POSTOPERATIVE LIVER DYSFUNCTION AFTER CARDIOPULMONARY BYPASS SURGERY: A PROSPECTIVE CASE-CONTROL STUDY

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Abstract

Background: The use of N-Acetylcysteine (NAC) in preventing postoperative liver dysfunction following on-pump cardiac surgery presents a novel approach to improving patient outcomes in this specific medical context. The objectives of studies investigating the prophylactic administration of NAC in patients undergoing cardiac surgeries with cardiopulmonary bypass (CPB) include assessing its impact on liver function and overall postoperative recovery. **Material and Methods:** Forty adult patients undergoing cardiopulmonary bypass (CPB) with a CPB duration longer than 120 minutes were included in the study. The patients were split into two groups: a control group and a study group that received NAC in accordance with procedure. Serum bilirubin, coagulation parameters, renal function tests, and liver enzymes (ALT, AST, and ALP) were assessed. The length of mechanical ventilation, amount of chest tube drainage, duration of the ICU stay, duration of the hospital stay, levels of bilirubin and liver enzymes, and other characteristics were evaluated. **Results:** The study revealed that patients in the group receiving NAC had significantly lower levels of liver enzymes (ALT, AST, ALP) and bilirubin compared to the control group. Patients who received NAC showed shorter durations of mechanical ventilation, total chest tube drainage, ICU stay, and hospital stay compared to those in the control group. **Conclusion:** Prophylactic intravenous NAC was found to have a protective role in preventing postoperative hepatic dysfunction in patients undergoing cardiac surgery with CPB.

INTRODUCTION

Several studies have highlighted the high incidence of postoperative liver dysfunction following cardiac surgeries with cardiopulmonary bypass (CPB), ranging from 10% to 35%, and its associated morbidity and mortality.[1] Prolonged cardiopulmonary bypass time (CPBT) has been identified as a significant predictor of postoperative liver dysfunction, underscoring the need for preventive measures.

The liver, a vital organ, is highly susceptible to damage during cardiopulmonary bypass (CPB), with factors like non-pulsatile perfusion, low-flow state, free radical formation, and increased catecholamine levels increasing the risk. Despite various agents proposed to reduce inflammation, none have been successful in preventing hepatic dysfunction.

N-Acetyl cysteine (NAC) was first used for treating paracetamol overdose in 1979 and has since been proven safe for nonacetaminophen-induced acute liver failure.[2] Prophylactic NAC use has been linked to reduced postoperative atrial fibrillation and all-cause mortality in cardiac surgery patients.[3] A meta-analysis found that NAC administration only reduced the risk of atrial fibrillation among other variables studied, but not hepatic injury prevention. The benefits of NAC administration in cardiac surgery remain unexplored.[4]

One study conducted a randomized, parallel-group, double-blinded interventional trial involving 60 adult patients undergoing cardiac surgeries with cardiopulmonary bypass (CPB). The study group receiving NAC showed significantly lower levels of liver enzymes and bilirubin compared to the control group. Additionally, patients in the NAC group had shorter durations of mechanical ventilation, chest tube drainage, ICU stay, and hospital stay, highlighting the protective role of prophylactic NAC in preventing postoperative hepatic dysfunction.[1]

These comparative studies provide valuable insights into the potential benefits of N-Acetylcysteine supplementation in reducing postoperative complications and improving recovery outcomes in patients undergoing cardiac surgeries with CPB. The findings support the use of prophylactic NAC as a promising intervention to mitigate postoperative complications and enhance patient care in the context of on-pump cardiac surgery.

However, to prove the above findings the present study is to investigate the prophylactic administration of NAC in patients undergoing cardiac surgeries with cardiopulmonary bypass (CPB) and assessing its impact on liver function and overall postoperative recovery.

MATERIALS AND METHODS

Study Design: Design a prospective case-control study to compare patients who receive prophylactic NAC with a control group to assess the impact on postoperative liver dysfunction following cardiopulmonary bypass surgery.

Participant Selection: Enroll consenting adult patients undergoing cardiac surgeries using cardiopulmonary bypass, with a focus on those at risk of postoperative liver dysfunction.

Randomization: Randomly assign patients into the study group (receiving NAC) and the control group (standard care) to ensure unbiased allocation.

Intervention: Administer NAC according to a predefined protocol to the study group starting preoperatively and continuing postoperatively for a specified duration.

Data Collection: Collect comprehensive data including patient demographics, preoperative liver function tests, surgical details, NAC administration details, postoperative liver function tests, length of hospital stay, and other relevant variables.

Outcome Measures: Evaluate primary outcomes such as the incidence of postoperative liver dysfunction, changes in liver function tests, coagulation parameters, renal function tests, and liver enzymes (ALT, AST, and ALP) were assessed. The length of mechanical ventilation, amount of chest tube drainage, duration of the ICU stay, duration of the hospital stay, levels of bilirubin and liver enzymes, and other characteristics were evaluated.

Follow-Up: Conduct regular follow-ups post-surgery to monitor patient outcomes, adherence to NAC treatment, and any adverse events related to NAC administration.

Ethical Considerations: The study ensures compliance with ethical guidelines, patient confidentiality, informed consent procedures, and institutional review board approval throughout the study.

Statistical Analysis: Statistical analysis was done using Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) was used. The difference in mean values and Chi-square test were utilised for categorical, and paired t-test and independent student t test were applied to compare the preoperative and postoperative liver function and renal function analysis and other parametric data. Significant difference was accepted at $P \leq .05$.

RESULTS

The study analyzed 40 patients divided into two groups of 20 each, comparing demographic and preoperative parameters between the prophylactic NAC group and the control group (Table 1). Table reveals that all parameters were comparable, indicating a homogeneous and comparable study population. Table 2 compares intraoperative parameters, surgery types, and blood product use between groups, including CPBT, aortic cross clamp time, total anesthesia duration, and minimum CBP temperature, among other factors.

Table 3 compares liver function tests between preoperative, postoperative, and postoperative groups. Results show comparable preoperative values, but significantly higher serum ALT, AST, and ALP values in the control group from surgery day to third postoperative day. Serum bilirubin levels were comparable until first postoperative day. The study found that INR and APTT were similar preoperatively, but the control group had significantly higher INR from the first to third postoperative day. The study found that serum creatinine, blood urea levels, and 24-hour urine output were comparable between the groups until the first postoperative day, but significantly higher in the control group from the day of surgery to the third postoperative day.

Table 4 shows the comparison of postoperative parameters between two groups. The mean duration of mechanical ventilation, duration of stay in hospital and duration of stay in ICU were significantly high in control group as compared to study group. The incidence of postoperative AF was also significantly high in control group as compared to study group.

Table 1: Comparison of Demographic and Preoperative Parameters between two groups

	Case (n=20)	Control (n=20)	*P*
Age (mean±SD) (years)	37±16.33	42.78±13.25	0.226
Male Gender	14 (70.0)	17 (85.0)	0.256
Height (cm)	153.44±6.78	157.54±8.45	0.098
Weight (kg)	52.47±9.7	51.58±9.54	0.771
Sinus rhythm	14 (70%)	16 (80%)	0.465
Pulmonary hypertension	17 (85.0)	14 (70.0)	0.256

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Diabetes mellitus	2 (3.33)	1 (3.33)	0.548
Systolic blood pressure (SBP)	117.25±9.23	116.87±10.25	0.902
Diastolic blood pressure (DBP)	64.58±11.45	63.54±11.82	0.779

Table 2: Comparison of Intraoperative Parameters between two groups

	Case (n=20)	Control (n=20)	*P*
Cardiopulmonary bypass time (minutes)	214.74±28.33	217.63±32.64	0.766
Aortic cross clamp time (minutes)	189.63±31.64	186±40.14	0.752
Duration of anaesthesia (hours)	3.86±50.01	3.87±59.43	0.999
Minimum temperature of CPB (°C)	29.10±0.332	29.03±0.26	0.462
Type of surgeries			
AVR	1 (5.0)	2 (10.0)	0.548
MVR	2	2	-
MVR + AVR	12 (60.0)	11 (55.0)	0.749
MVR + TA	1	1	-
Redo MV	1	1	-
VSD + PDA	1	1	-
CABG	2	2	-
Intraoperative blood transfusion			
PRBC	0.33±0.54	0.40±0.498	0.670
FFP	3.3±0.65	3.17±0.699	0.546
RDP	3.40±0.62	3.30±0.65	0.621

Table 3: Comparison of mean changes in LFT, coagulation parameters, kidney function test and 24 hours urine output between the groups

	Case (n=20)	Control (n=20)	P
Serum AST			
Preop	33.25±17.41	38.52±16.51	0.33
Day 3	48.71±33.51	487.52±32.76	<0.001
Serum ALT			
Preop	25.31±14.54	28.73±16.26	0.487
Day 3	63.51±13.44	630.45±11.67	<0.001
Serum ALKP			
Preop	96.54±30.71	94.87±30.64	0.864
Day 3	72.63±54.58	124.96±61.86	0.007
Serum Total Bilirubin			
Preop	0.99±0.32	0.82±0.29	0.086
Day 3	1.13±0.61	2.63±1.12	<0.001
Serum direct bilirubin			
Preop	0.21±0.15	0.24±0.11	0.475
Day 3	0.51±0.30	1.12±0.63	0.0003
INR			
Preop	1.18±0.161	1.13±0.16	0.640
Day 3	1.36±0.18	1.51±0.21	0.020
APTT (seconds)			
Preop	26.74±1.36	25.81±1.59	0.054
Day 3	27.7±2.15	30.41±3.63	0.006
Platelet count			
Preop	1.22±0.54	1.31±0.54	0.601
Day 3	1.18±0.36	1.25±0.56	0.640
Serum Creatinine			
Preop	0.88±0.63	1.02±0.206	0.350
Day 3	1.21±0.54	1.88±0.89	0.006
Serum Urea			
Preop	28.74±5.24	29.68±5.84	0.595
Day 3	36.57±18.51	71.58±39.44	0.009
24 Hours Urine Output			
Preop	1.74±0.36	1.61±0.33	0.241
Day 3	1.55±0.41	0.74±0.38	<0.001

Table 4: Comparison of postoperative parameters between the Two Groups

Postoperative Parameters	Case (n=20)	Control (n=20)	*P*
Duration of mechanical ventilation (hours)	9.64±3.11	19.21±11.54	<0.001
Duration of stay in hospital (days)	5.41±0.63	7.87±1.55	<0.001
Duration of stay in ICU (hours)	9.55±0.69	14.51±2.21	<0.001
Incidence of postoperative AF	8 (40.0)	16 (80.0)	0.009

DISCUSSION

In the context of the study on " N-Acetylcysteine for the Prevention of Postoperative Liver Dysfunction after On-Pump Cardiac Surgery " and in comparison with other relevant studies, the variables of age, male gender, height, weight, sinus rhythm, pulmonary hypertension, diabetes mellitus, systolic

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blood pressure, and diastolic blood pressure were found to be comparable between cases and controls.

The impact of Cardiopulmonary Bypass Time (CPBT) after cardiopulmonary bypass surgery is crucial in determining postoperative outcomes, particularly mortality and morbidity rates. Studies have shown that prolonged CPBT can significantly affect patient outcomes, leading to adverse events such as prolonged mechanical ventilation, renal failure, stroke, and reoperation. Additionally, very-long CPBT times have been associated with high rates of operative mortality and morbidity, emphasizing the importance of monitoring and managing CPBT duration during cardiac operations.[5,6] Furthermore, research indicates that CPBT duration correlates strongly with prolonged mechanical ventilation, with CPBT being the most significant variable affecting clinical outcomes. Avoiding or minimizing CPB time may reduce the duration of mechanical ventilation required postoperatively, highlighting the potential benefits of limiting CPBT to improve patient recovery and reduce complications.[6]

The impact of Aortic Cross Clamp Time (XCT) after cardiopulmonary bypass surgery is crucial in determining postoperative outcomes, particularly mortality and morbidity rates. Studies have consistently shown that prolonged XCT significantly correlates with major postoperative morbidity and mortality in both low- and high-risk cardiac surgery patients. Prolonged XCT is an independent predictor of adverse outcomes, including increased risks of operative mortality, morbidity, and complications following cardiac surgery.[7,8]

Prolonged anesthesia duration can contribute to delayed recovery, which is a significant concern in patients undergoing cardiac surgery with cardiopulmonary bypass. Studies have shown that the time to recovery of consciousness in adult patients undergoing elective cardiac surgery can be affected by factors such as the duration of cardiopulmonary bypass, with longer CPB times leading to increased time to recovery of consciousness.[9]

The impact of the Minimum Temperature of Cardiopulmonary Bypass (CPB) after cardiopulmonary bypass surgery is crucial in determining postoperative outcomes, particularly in relation to cerebral and renal function. Maintaining optimal CPB temperatures is essential for patient safety and recovery. Studies have shown that hypothermia during CPB can be used for organ protection by reducing metabolic activity and protecting cerebral metabolism.[10,11]

A retrospective observational study highlighted that the type of surgery was a significant predictor of complications in patients undergoing cardiac surgery under CPB. The study identified that factors such as gender, body weight, blood lactate levels, and the type of surgery were associated with postoperative complications. Specific surgeries were linked to prolonged ICU and hospital length of stay, indicating that the type of surgery plays a crucial role in determining patient outcomes.[12]

Research has shown that intraoperative blood transfusion during noncardiac surgery is linked to a higher risk of 30-day mortality. Patients who received intraoperative transfusions were found to have an increased risk of death compared to those who did not receive transfusions. The odds ratio for mortality was reported to be 1.29, indicating a significant association between intraoperative blood transfusion and mortality.[13]

In the present we compare intraoperative parameters, surgery types, and blood product use between groups, including CPBT, aortic cross clamp time, total anesthesia duration, and minimum CBP temperature, among other factors. No significant difference were observed between cases and controls.

Postoperative liver function tests following open cardiac surgery can show transient alterations in hepatic enzymes. Studies have indicated that there can be a significant increase in total bilirubin, aspartate aminotransferase (AST), and alkaline phosphatase levels in the third postoperative day. These changes are attributed to factors like hypoxia or pump-induced inflammation, leading to temporary alterations in hepatic enzymes.[14]

Managing the coagulopathy associated with cardiopulmonary bypass surgery is crucial for patient outcomes. Understanding the etiology of coagulopathy facilitates management and can improve outcomes post-surgery. Coagulopathy associated with cardiac surgery can have implications for patient recovery and overall surgical success.[15]

The impact of cardiopulmonary bypass perfusion temperature on perioperative renal function has been studied. Results have shown that varying CPB perfusion temperatures (28°C, 32°C, and 37°C) did not significantly influence renal function in patients undergoing routine surgeries. This suggests that CPB perfusion temperature may not have a substantial impact on perioperative renal function in this context.[16]

While the specific impact of 24-hour urine output after cardiopulmonary bypass surgery is not directly addressed in the provided sources, monitoring urine output postoperatively is a standard practice to assess renal function and fluid balance. Adequate urine output is essential for evaluating kidney function and ensuring proper fluid management following cardiac surgery with CPB.

In the present study results show comparable preoperative values, but significantly higher serum ALT, AST, and ALP values in the control group from surgery day to third postoperative day. Serum bilirubin levels were comparable until first postoperative day. The study found that INR and APTT were similar preoperatively, but the control group had significantly higher INR from the first to third postoperative day. The study found that serum

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creatinine, blood urea levels, and 24-hour urine output were comparable between the groups until the first postoperative day, but significantly higher in the control group from the day of surgery to the third postoperative day.

Prolonged cardiopulmonary bypass time is associated with prolonged mechanical ventilation post-surgery. Studies have shown that CPB time correlates with prolonged mechanical ventilation, with CPB time being the most strongly correlated variable. Avoiding or minimizing CPB time may reduce the duration of mechanical ventilation required.[6]

Longer CPB time has been linked to poorer clinical outcomes, including longer lengths of stay in the ICU and hospital. Patients with extended CPB time had higher ICU and in-hospital mortality rates compared to those with shorter CPB times. For each ten-minute increment in CPB time, the risks of worse outcomes increased significantly, indicating the impact of CPB time on patient recovery and hospital stay.[17]

Postoperative Atrial Fibrillation (AF) is considered an indication for keeping patients in the ICU. Factors like prolonged ventilatory support, postoperative pneumonia, and not using beta-blockers before surgery have been associated with prolonged ICU stays after cardiac surgery. Postoperative pneumonia and the absence of beta-blocker use preoperatively have been shown to predict longer ICU stays, highlighting the impact of these factors on patient outcomes post-CPB surgery.[18]

The study's limitations include a small sample size, a single-center focus, and a short follow-up period, which could affect the generalizability of results and the ability to assess long-term outcomes related to postoperative liver dysfunction and the effectiveness of N-Acetylcysteine in preventing complications over an extended period.

CONCLUSION

The study found that prophylactic intravenous N-Acetylcysteine (NAC) significantly improves postoperative liver dysfunction in patients undergoing cardiopulmonary bypass (CPB) cardiac surgery. Patients receiving NAC had lower liver enzyme values, lower serum bilirubin levels, shorter mechanical ventilation, ICU, and hospital stays, and lower incidence of postoperative atrial fibrillation. These findings support NAC's effectiveness in mitigating liver dysfunction and improving overall outcomes.

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